VOLUME 31 · NUMBER 2 · JANUARY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gonadal Function and Fertility in Survivors After Hodgkin Lymphoma Treatment Within the German Hodgkin Study Group HD13 to HD15 Trials

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Published online ahead of print at www.jco.org on November 13, 2012.

Written on behalf of the German Hodgkin Study Group.

Supported by the Deutsche Krebshilfe (Grant No. 109087), the Bundesministerium für Bildung und Forschung, and the Kompetenznetz Maligne Lymphome.

Presented in part at 53rd Annual Meeting of the American Society of Hematology, December 10-13, 2011, San Diego, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3102-231/$20.00

DOI: 10.1200/JCO.2012.44.3721

ABSTRACT

Purpose
To optimize fertility advice in patients with Hodgkin lymphoma (HL) before therapy and during survivorship, information on the impact of chemotherapy is needed. Therefore, we analyzed gonadal functions in survivors of HL.

Patients and Methods
Women younger than age 40 and men younger than 50 years at diagnosis in ongoing remission at least 1 year after therapy within the German Hodgkin Study Group HD13 to HD15 trials for early- and advanced-stage HL were included. Hormone parameters, menstrual cycle, symptoms of hypogonadism, and offspring were evaluated.

Results
A total of 1,323 (55%) of 2,412 contacted female and male survivors were evaluable for the current analysis (mean follow-up, 46 and 48 months, respectively). Follicle-stimulating hormone, anti-Müllerian hormone, and inhibin B levels correlated significantly with therapy intensity ($P < .001$). Low birth rates were observed in survivors after advanced-stage treatment within the observation time (women, 6.5%; men, 3.3%). Regular menstrual cycle was reported by more than 90% of female survivors of early-stage HL (recovery time mostly ≤ 12 months). After six to eight cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, menstrual activity was strongly related to age (< *v* ≥ 30 years: 82% *v* 45%, respectively; $P < .001$; prolonged recovery time). Thirty-four percent of women age ≥ 30 years suffered severe menopausal symptoms (three- to four-fold more frequently than expected). In contrast, male survivors had mean levels of testosterone within the normal range and reported no increased symptoms of hypogonadism.

Conclusion
The present analysis in a large group of survivors of HL provides well-grounded information on gonadal toxicity of currently used treatment regimens and allows risk-adapted fertility preservation and comprehensive support during therapy and follow-up.

J Clin Oncol 31:231-239. © 2012 by American Society of Clinical Oncology

INTRODUCTION

High overall survival rates (approximately 90%) in early- and advanced-stage Hodgkin lymphoma (HL) have been achieved.[1-3] Thus, current clinical research focuses on the short- and long-term sequelae in the growing number of young survivors of HL. Among these sequelae, infertility and hypogonadism are of particular importance for patients and survivors and demand specialized medical care.[4-8]

Health care professionals need comprehensive information on treatment-related gonadal toxicity. At diagnosis, physicians should inform the patient thoroughly and consider protective methods to preserve fertility in time. During the follow-up period, survivors need professional advice when they desire to have children. Furthermore, it is essential to detect and maybe to treat symptoms of hypogonadism. Unfortunately, these issues are still not routinely addressed by most physicians.[5,9]

It is known that the rate of treatment-induced infertility increases with more aggressive chemotherapy.[10-14] However, there still are many open questions about the probability of amenorrhea, reduced ovarian reserve, and infertility after distinct chemotherapies and the impact of age at treatment onset, as

well as about the chance of recovery and the risk of suffering from symptoms of hypogonadism. Thus, more detailed information is needed for both patients and physicians. Therefore, the main objective of the present analysis is to provide data on the impact of currently used chemotherapy in HL on gonadal function.

PATIENTS AND METHODS

HD13 to HD15 Trials: Patients and Study Design

Patients (age 18 to 75 years) with biopsy-proven HL were included in trials for early favorable (HD13, two cycles of doxorubicin, vinblastine, and dacarbazine with bleomycin [ABVD] or without bleomycin), early unfavorable (HD14, arm A: four cycles of ABVD or arm B: two cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone [BEACOPP] followed by two cycles of ABVD [2+2]), or advanced-stage HL (HD15, six to eight cycles of escalated BEACOPP or eight cycles of BEACOPP-14).[1-3] The studies were carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Assessment of Gonadal Function and Fertility

All survivors (age at random assignment: women, 18 to 39 years; men, 18 to 49 years) in ongoing remission at least 1 year after therapy and without any other treatment than the HD13 to HD15 trial medication were addressed. In women, results were stratified with respect to age (cutoff, 30 years).[12,15] In men, we interpreted inhibin B in the context of follicle-stimulating hormone (FSH) levels to achieve the highest positive predictive value with a cutoff for the inhibin B/FSH ratio corresponding to proven fertile men and cutoff levels for FSH and inhibin B corresponding to oligospermia.[16,17]

Questionnaires

Symptoms of hypogonadism were determined using the Menopause Rating Scale (MRS) and the Aging Males' Symptoms scale.[18-21] Additional questions referred to the use of hormonal substitution, methods of fertility preservation before therapy, menstrual status, pregnancies and offspring after normal and in vitro fertilization, and social aspects.

Hormone Analysis

Survivors were asked to take a blood sample (samples for women were taken on day 3 of a new menstrual cycle or at the end of the pill break). Blood samples were then centrally processed and stored at −80°C until analysis. Tests included standardized assays for FSH, luteinizing hormone (LH), estradiol, and testosterone (heterogenic, noncompetitive chemiluminescent immunometric assays; Elecsys-FSH, Elecsys-LH, Elecsys-Estradiol-II, Elecsys-Testosterone-II; Roche Diagnostics, Mannheim, Germany); anti-Müllerian hormone (AMH; active AMH Gen-II ELISA; Beckman Coulter, Prague, Czech Republic); and inhibin B (inhibin B Gen-II ELISA-KIT; Beckman Coulter).

Statistics

In female survivors (≤ 40 years old at first diagnosis of HL and ≤ 45 years old at time of fertility assessment), results are reported in age groups (18 to 29 years and 30 to 45 years). For men, the upper age limit at time of fertility assessment was 57 years. Outcome measures of female fertility were menstrual activity, time to resumption of menstrual activity, hormone values, MRS, offspring, and pregnancies after therapy. Hormone levels were natural log-transformed before statistical computations to normalize distributions. Fertility parameters in HD15 survivors are additionally stratified for the use of gonadotropin-releasing hormone (GnRH) analogs. Results are presented with descriptive statistics and 95% CIs. To provide a more detailed analysis of age effects in female survivors, we computed a logistic regression of amenorrhea on age, with time since end of chemotherapy as covariate. Additionally, generalized Kaplan-Meier estimates of time to resumption of menstrual activity are provided for age groups. For analyses of male survivors, FSH and LH were log-transformed before any statistical computations; inhibin B, testosterone, and the inhibin B/FSH ratio were not transformed because these variables and their residuals showed no major deviations from normality. Correlations between hormone levels and relevant parameters such as age or follow-up time were assessed using linear regression models within treatment groups.

The level of significance was set at $P = .05$ (two-sided). Continuous parameters were tested with parametric tests for independent groups (t test, analysis of variance), categorical data were tested with exact and binomial tests, and no corrections for multiple testing were applied. All statistical analyses were computed with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 1,323 (55%) of 2,412 contacted survivors participated (562 women and 761 men; Fig 1). In women and men, mean age at fertility assessment was 32 and 38 years, respectively, and mean observation time from the end of treatment was 46 and 48 months, respectively. Comparing all trials, there were unfavorable conditions for patients treated in the HD13 trial, with higher age at fertility assessment (women, 36 years; men, 40 years) and a higher proportion of patients having children before therapy (women, 47%; men, 57%). There were balanced conditions for patients treated in the HD14 and HD15 trials (Table 1). Comparison of the participating and nonparticipating patients qualifying for our analysis showed no relevant differences (Appendix Table A1, online only).

Female Survivors

Hormones in female survivors. Differences in favor of early-stage patients treated with fewer cycles (two to four instead of six to eight cycles) of less intensive chemotherapy were high and significant for AMH and FSH in both age groups ($P < .001$). Hormone levels were

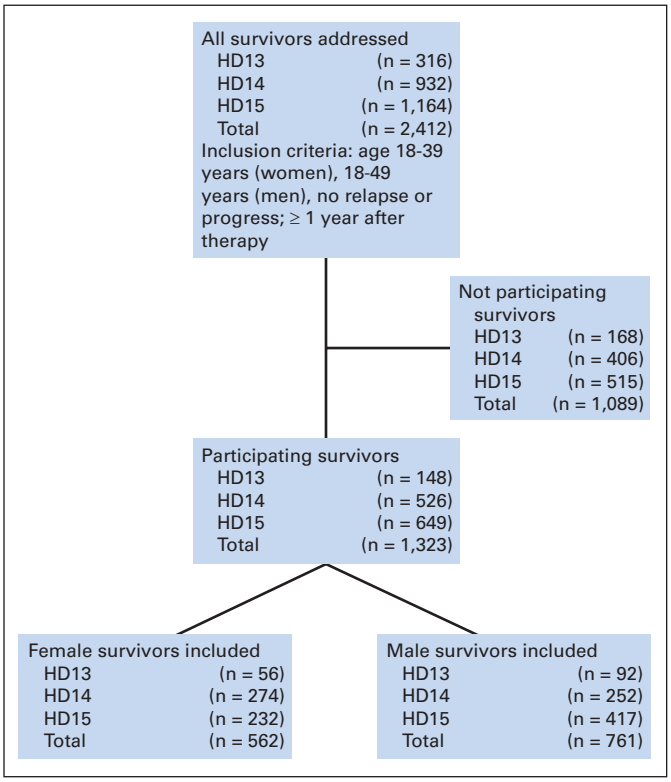

Fig 1. CONSORT diagram.

Table 1. Patient Characteristics

Characteristic	Female Patients								Male Patients							
	HD13 (n = 56)		HD14 (n = 274)		HD15 (n = 232)		Total (n = 562)		Total (n = 761)		HD13 (n = 92)		HD14 (n = 252)		HD15 (n = 417)	
	No./Total No.*	%*	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%
Age at fertility assessment, years																
Mean	35		32		32		32		38		40		37		38	
Standard deviation	7		7		7		7		9		8		9		9	
Range	21-44		20-45		20-45		20-45		19-57		21-54		19-54		20-57	
Age at HL diagnosis, years																
Mean	31		28		27		28		34		36		34		33	
Standard deviation	6		7		6		7		9		9		9		9	
Range	18-39		18-39		18-39		18-39		18-49		18-49		18-49		18-49	
Time from end of chemotherapy, months																
Mean	45		43		50		46		48		50		44		51	
Standard deviation	23		20		20		20		20		24		19		19	
Range	12-96		12-83		12-91		12-96		12-103		12-103		12-79		12-94	
Clinical stage																
I	4/45	9	10/274	4			14/549	2	36/736	5	25/68	37	11/251	4		
II	41/45	91	260/274	96	59/230	26	364/549	66	341/736	46	43/68	63	240/251	96	58/417	14
III					105/230	46	105/549	19	225/736	31					225/417	54
IV					66/230	29	66/549	12	134/736	18					134/417	32
"B" symptoms present	7/45	16	56/274	20	145/230	63	208/549	38	362/736	49	8/68	12	81/251	32	273/417	66
Chemotherapy																
Two cycles of A(B)VD	56/56	100					56/562	10	92/761	12	92/92	100				
Four cycles of ABVD			139/274	51			139/562	25	120/761	16			120/252	48		
2+2			135/274	49			132/562	23	132/761	17			132/252	52		
Eight cycles of escalated BEACOPP					79/232	34	79/562	14	142/761	19					142/417	34
Six cycles of escalated BEACOPP					75/232	32	75/562	13	146/761	19					146/417	35
Eight cycles of BEACOPP-14					79/232	34	79/562	14	129/761	17					129/417	31
Parenthood before, yes	23/49	47	96/255	38	85/219	39	204/523	39	323/705	46	50/88	57	101/233	43	172/384	45
Oral contraception, yes	15/54	28	86/268	32	46/231	20	147/553	27								
GnRH, yes	10/54	19	62/268	23	77/231	33	149/553	27								
Oral contraception now, yes	25/54	46	131/268	49	134/231	58	290/553	52								
Cryopreservation of sperm (men) or oocytes or ovarian tissue (women), yes†	3/52	6	21/257	8	20/214	8	44/523	9	274/724	38	26/88	30	101/239	42	147/397	37
Sex partner now, yes	52/55	95	240/265	91	174/219	80	466/539	87	593/713	83	76/86	88	197/236	84	320/391	82

Abbreviations: A(B)VD, doxorubicin, (bleomycin), vinblastine, and dacarbazine; ART, assisted reproduction; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; GnRH, gonadotropin-releasing hormone; HL, Hodgkin lymphoma; 2+2, two cycles of BEACOPP followed by two cycles of ABVD.

*Total No. represents number of patients with valid data, and percentages represent percentages of patients with valid data.

†Cryopreservation of fertilized oocytes, n = 6; cryopreservation of unfertilized oocytes, n = 11; cryopreservation of oocytes not further specified, n = 4; cryopreservation of ovarian tissue, n = 16; cryopreservation of both oocytes and ovarian tissue, n = 1; and cryopreservation not further specified, n = 6.

different with respect to age; mean AMH levels greater than 2 μg/L were only observed in women younger than 30 years after ABVD therapy (Table 2). After HD15 therapy, mean AMH levels were 0 μg/L in both age groups, and the highest FSH levels were measured (mean FSH: $<$ 30 years, 11.1 U/L; $\geq$ 30 years, 29.7 U/L). Serum levels of AMH and FSH differed between treatment groups in the HD14 trial. These differences in favor of ABVD were high and significant for FSH in older women (mean FSH in women age 30 to 45 years: arm A, 4.4 U/L; arm B, 11.8 U/L; $P < .001$) and for AMH in both age groups (mean AMH in women age $<$ 30 years: arm A, 2.3 μg/L; arm B, 0.9 μg/L; $P < .001$; mean AMH in women age $\geq$ 30 years: arm A, 0.7 μg/L; arm B, 0.0 μg/L; $P < .001$).[22] In contrast, no difference was found between the three BEACOPP arms of the HD15 trial ($P > .15$).

Regular cycle and time to resumption of menstrual activity. In both age groups, more than 90% of survivors after treatment for early-stage HL reported a regular cycle after therapy, and time to resumption of menstrual activity was mostly reached within 1 year (Fig 2A). After treatment for advanced-stage HL, 82% of women younger than 30 years had a regular cycle, compared with only 45% of women in the older age group (Table 2). There was no difference regarding whether or not women had received cotreatment with GnRH analogs. Time to resumption of menstrual activity took considerably longer than in early-stage patients and was strongly related to age (Fig 2A). The mean age of women with sustained amenorrhea was 31.6 years at start of chemotherapy (95% CI, 30.5 to 32.8 years), whereas the mean age of women with a regular cycle was 27.1 years

Table 2. Fertility Parameters of Female Survivors After Six Randomly Assigned Treatments in Two Age Groups (18 to 29 years and 30 to 45 years)

Parameter	HD13: Two Cycles of A(B)VD		HD14				HD15									
			Four Cycles of ABVD		2+2		Eight Cycles of Escalated BEACOPP		Six Cycles of Escalated BEACOPP		Eight Cycles of BEACOPP-14		HD15† GnRH		HD15† No GnRH	
	No./Total No.*	%*	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%
Age 30-45 years	39		88		72		38		46		50		34		100	
Hormones																
AMH, μg/L‡																
Mean	0.7		0.7		0.0		0.0		0.0		0.0		0.0		0.0	
95% CI	0.3 to 1.6		0.5 to 1.1		0.0 to 0.1		0.0 to 0.0		0.0 to 0.0		0.0 to 0.1		0.0 to 0.1		0.0 to 0.0	
FSH, U/L‡																
Mean	7.5		4.4		11.8		41.2		23.6		29.3		25.9		31.5	
95% CI	5.9 to 9.6		3.4 to 5.8		8.2 to 16.9		28.2 to 60.2		14.6 to 38.2		20.3 to 42.2		15.4 to 43.7		24.1 to 41.1	
FSH, U/L‡ (sensitivity§)																
Mean	6.9		5.1		10.7		41.4		28.8		34.5		23.8		38.0	
95% CI	5.1 to 9.3		3.8 to 6.8		7.1 to 16.3		25.7 to 66.7		16.0 to 52.1		20.3 to 58.8		11.3 to 50.2		27.3 to 53.0	
Menopausal symptoms																
MRS total score																
Mean	9.0		9.0		9.6		12.2		11.5		12.6		10.4		12.7	
95% CI	6.1 to 12.0		7.3 to 10.8		7.6 to 11.6		9.0 to 15.4		8.3 to 4.6		10.0 to 15.2		7.1 to 13.8		10.7 to 14.6	
MRS severity‖																
Severe (8%)	7/29	25	14/66	21	13/54	24	13/32	41	11/39	29	13/39	33	8/28	30	29/82	35
Moderate (20%)	5/29	18	12/66	18	10/54	19	6/32	19	11/39	29	15/39	38	5/28	19	27/82	33
Mild (25%)	6/29	21	20/66	30	15/54	28	4/32	13	7/39	18	3/39	8	7/28	26	7/82	9
No/few (48%)	10/29	36	20/66	30	16/54	30	9/32	28	9/39	24	8/39	21	7/28	26	19/82	23
Regular cycle after therapy	36/37	97	77/82	94	65/72	90	13/37	35	24/44	55	22/50	44	16/34	47	43/97	44
Regular cycle after therapy (sensitivity§)	25/26	96	57/61	93	47/53	89	9/26	35	16/31	52	11/27	41	10/19	53	26/65	40
Regular cycle presently	35/37	95	69/82	84	54/72	75	14/37	38	18/45	40	24/50	48	15/33	45	41/99	41
Regular cycle presently (sensitivity§)	24/26	92	51/61	84	40/53	75	8/27	30	8/31	26	9/27	33	7/19	37	18/66	27
Pregnancy	6/35	17	14/82	17	20/71	28	4/36	11	5/44	11	4/49	8	3/32	9	10/97	10
Birth	3/31	10	9/76	12	16/62	26	4/36	11	2/42	5	2/46	4	2/31	6	6/93	6
Age 18 to 29 years	17		51		63		41		28		29		43		53	
Hormones																
AMH, μg/L‡																
Mean	2.2		2.3		0.9		0.0		0.1		0.0		0.0		0.1	
95% CI	1.4 to 3.6		1.5 to 3.5		0.7 to 1.2		0.0 to 0.1		0.1 to 0.2		0.0 to 0.1		0.0 to 0.1		0.0 to 0.1	
FSH, U/L‡																
Mean	2.4		3.1		4.4		9.8		10.6		13.5		13.6		9.4	
95% CI	1.2 to 4.7		2.2 to 4.5		3.2 to 6.1		6.1 to 16.0		6.3 to 18.0		8.3 to 22.1		8.7 to 21.3		6.4 to 13.7	
FSH, U/L‡ (sensitivity§)																
Mean	2.3		3.9		3.2		12.1		9.9		13.6		13.1		10.8	
95% CI	0.8 to 6.7		2.3 to 6.7		1.7 to 5.8		5.8 to 24.9		4.7 to 20.6		6.8 to 26.9		6.2 to 27.8		6.9 to 17.0	
Menopausal symptoms																
MRS total score																
Mean	6.2		7.1		6.3		9.6		8.3		8.9		9.2		8.9	
95% CI	3.3 to 9.1		5.2 to 9.0		4.3 to 8.2		7.0 to 12.2		5.4 to 11.1		4.8 to 13.0		6.8 to 11.6		6.4 to 11.3	
MRS severity‖																
Severe (8%)	0/13	0	6/40	15	3/47	6	5/29	17	2/21	10	3/20	15	3/30	10	7/40	18
Moderate (20%)	4/13	31	6/40	15	10/47	21	12/29	41	6/21	29	4/20	20	13/30	43	9/40	23
Mild (25%)	4/13	31	13/40	33	10/47	21	5/29	17	6/21	29	6/20	30	7/30	23	10/40	25
No/few (48%)	5/13	38	15/40	38	24/47	51	7/29	24	7/21	33	7/20	35	7/30	23	14/40	35
Regular cycle after therapy	15/16	94	49/49	100	60/60	100	33/39	85	23/26	88	19/27	70	33/43	77	42/49	86
Regular cycle after therapy (sensitivity§)	8/9	89	21/21	100	29/29	100	16/20	80	14/16	88	12/15	80	26/30	87	16/21	76
Regular cycle presently	14/16	88	45/49	92	59/62	95	34/40	85	21/26	81	25/29	86	36/43	84	44/52	85
Regular cycle presently (sensitivity§)	8/9	89	19/21	90	28/30	93	16/20	80	13/17	76	13/15	87	16/21	76	26/30	87
Pregnancy	1/16	6	7/50	14	12/60	20	3/40	8	5/27	19	1/28	4	3/43	7	6/52	12
Birth	1/15	7	6/43	14	6/48	13	2/38	5	3/26	12	1/27	4	2/42	5	4/49	8

Abbreviations: A(B)VD, doxorubicin, (bleomycin), vinblastine, and dacarbazine; AMH, anti-Müllerian hormone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; MRS, Menopause Rating Scale; 2+2, two cycles of BEACOPP followed by two cycles of ABVD.

*Total No. represents number of patients with valid data, and percentages represent percentages of patients with valid data.

†Survivors of the HD15 study grouped according to (nonrandomized) treatment with GnRH.

‡All computations for AMH and FSH are log-transformed values to normalize distributions; table entries are in original units (after exponentiation).

§Sensitivity analysis in a subgroup of survivors who did not take oral contraceptives/hormone replacement therapy.

‖Classification of MRS total score with reference scores for 45- to 60-year-old German women in parentheses.

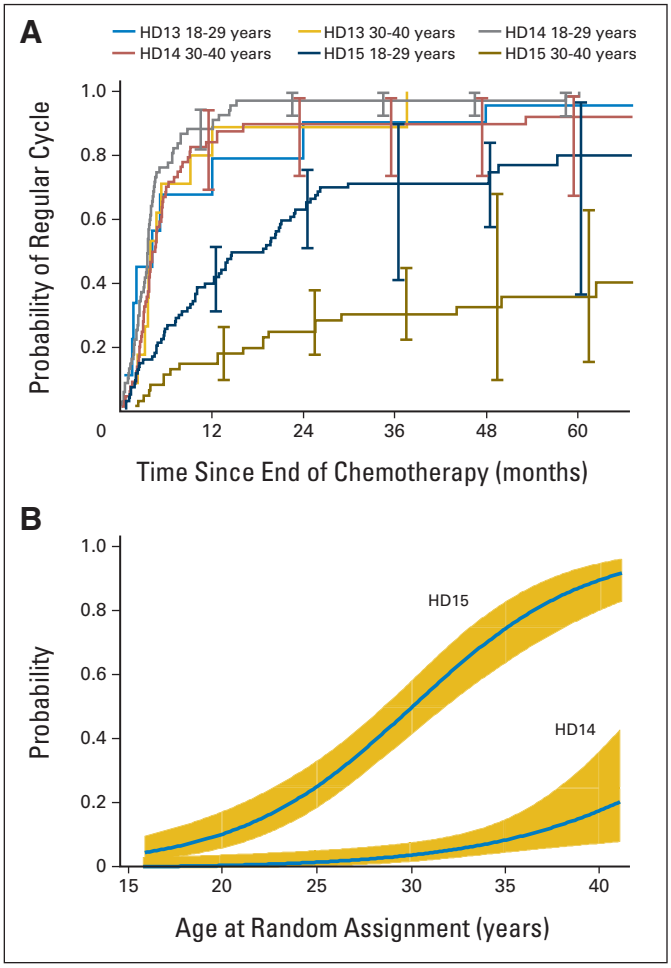

Fig 2. (A) Time to regular cycle in the three trials and two age groups. Generalized Kaplan-Meier estimates shown with 90% CIs for HD14 and HD15. (B) Probability of amenorrhea 4 years after chemotherapy; the significant influence of age at therapy is shown (estimates of logistic regression analyses for HD15 and HD14 at the mean time after chemotherapy, 47 months, with 90% CIs).

(95% CI, 26.5 to 27.7 years). In advanced-stage patients, the risk of amenorrhea 4 years after chemotherapy highly correlated with age at HL diagnosis (25 years = 25% risk; 30 years = 50% risk; Fig 2B). In the HD15 trial, only three (9%) of 35 women older than 35 years at start of chemotherapy reported a regular cycle after therapy, and in arms A and B, after six to eight cycles of escalated BEACOPP, only one (4%) of 23 survivors reported a regular cycle.

Pregnancies and Offspring

In contrast to women after treatment for early-stage HL, fewer pregnancies were reported in women after treatment for advanced-stage HL (HD13 + HD14, n = 60, 19%; HD15, n = 22, 10%; Table 2). After HD15 therapy, 51.9% of female survivors reported a desire to have children, but only 15% reported parenthood at 4 years. In advanced-stage patients, GnRH analogs had no influence on pregnancies after therapy in contrast to observed results after treatment for early unfavorable HL.[22]

Menopausal symptoms. MRS total score showed no significant difference between HL trials regarding menopausal symptoms in women $\leq$ 30 years. An age-related increase of severe menopausal symptoms was observed in all trials. Severe symptoms were four- to five-fold more frequent in women $\geq$ 30 years after therapy for advanced-stage HL compared with a 45- to 60-year-old German reference cohort (Table 2). MRS correlated significantly with menstrual activity ($P < .001$), as well as with LH and FSH levels ($P < .001$). Only 48.9% of women with severe symptoms were on hormone medication at the time of the survey.

Male Survivors

Hormones in male survivors. Serum levels of inhibin B and FSH were significantly different between trials in favor of early-stage patients treated with fewer cycles (two to four instead of six to eight cycles) of less intensive chemotherapy ($P < .001$). Importantly, in the HD14 trial, FSH and inhibin B values differed significantly between treatment arms in favor of ABVD. No difference was found between the three BEACOPP regimens in HD15 (Table 3).

With few exceptions, inhibin B and FSH levels corresponding to proven fertility (inhibin B/FSH ratio > 23.5 ng/U) were only seen after ABVD or 2+2 (HD13, 51.2%; HD14, 50.4%; HD15, 0.5%). The highest proportions of inhibin B and FSH levels corresponding to oligospermia (inhibin B < 80 ng/L and FSH > 10 U/L) were measured after BEACOPP (HD13, 12.2%; HD14, 20.7%; HD15, 88.8%; Fig 3A). LH levels increased significantly with disease stage (highest mean value of 7.3 U/L after HD15 treatment; normal range, 1.7 to 8.6 U/L). Mean testosterone levels were within the normal range of 2.8 to 8.0 ng/L after all treatment regimens (Table 3).

Effect of follow-up time and age on inhibin B and FSH levels. A significant effect of follow-up time on inhibin B and FSH levels, indicating a recovery of spermatogenesis, was found after treatment with the 2+2 regimen ($P < .001$). Overall, in the HD14 trial, these hormone levels differed significantly in favor of four cycles of ABVD ($P < .001$); however, the subgroup of survivors with a follow-up of $\geq$ 4 years showed similar hormone levels in both treatment groups (Fig 4). No recovery was found in survivors of advanced-stage HL. There was an effect of age in all three trials, with favorable hormone levels in younger survivors (HD13: $P = .08$; HD14: $P < .001$; HD15: $P < .001$; data not shown).

Effect of age on testosterone. In survivors after HD14 and HD15 treatment, a significant age effect was found, with higher testosterone levels in younger men (HD14: $P = .002$; HD15: $P < .001$). In a multivariate analysis adjusting for the effect of study, age remained an independent predictor of testosterone value (data not shown).

Utilization of cryopreserved sperm, birth rate, and children after therapy. The birth rate after treatment in the HD15 trial was significantly lower compared with after treatment for early stages (study comparison: $P = .04$). Children after natural fertilization were most frequently reported in survivors after early-stage therapy compared with advanced-stage therapy (22 *v* two children, respectively, in HD15; Fig 3B). Two hundred seventy-four male survivors (38%) underwent a cryopreservation of sperm before therapy (Table 1). The proportion was highest (71%) in 18- to 29-year-old men. Twenty-six of these survivors (10%) used their cryopreserved sperm for assisted reproduction (21 survivors of advanced-stage HL). Thirty-two percent of male survivors after HD15 therapy reported desire for children, but only 12% reported parenthood at a median follow-up time of 4 years.

Aging Males' Symptoms scale. Aging male symptoms were not different between patients in the trials and reference values (Table 3). No correlation between symptoms and hormonal levels, especially testosterone, was found.

Table 3. Results of Male Survivors

Parameter	HD13: Two Cycles of A(B)VD (n = 92)		HD14				HD15								Total (N = 761)	
			Four Cycles of ABVD (n = 120)		2+2 (n = 132)		Eight Cycles of Escalated BEACOPP (n = 142)		Six Cycles of Escalated BEACOPP (n = 146)		Eight Cycles of BEACOPP-14 (n = 129)					
	No./Total No.*	%*	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%	No./Total No.	%			No./Total No.	%
Hormones																
FSH, U/L																
Mean	5.6		4.4		7.9		19.2		18.7		19.0				11.0	
95% CI	4.8 to 6.6		3.9 to 4.9		6.8 to 9.1		17.6 to 21.0		17.3 to 20.3		17.4 to 20.8				10.3 to 11.7	
> 12.4 U/L	11/84	13	7/116	6	38/130	29	105/128	82	109/137	80	95/113	84			365/708	52
Inhibin B, ng/L																
Mean	126.1		162.5		93.9		15.9		16.9		15.4				67.2	
95% CI	111.5 to 140.7		149.1 to 176.0		80.5 to 107.2		11.3 to 20.4		12.9 to 20.9		11.4 to 19.3				61.4 to 73.0	
< 25 ng/L	6/82	7	4/117	3	28/130	22	100/130	77	104/139	75	80/112	71			322/710	45
Inhibin B/FSH ratio, ng/U																
Mean	33.4		49.1		25.8		1.5		1.5		1.4				17.5	
95% CI	26.0 to 40.8		41.3 to 57.0		18.7 to 32.9		0.8 to 2.1		1.0 to 2.0		0.9 to 1.9				15.1 to 20.0	
LH, U/L																
Mean	4.8		4.2		5.1		7.4		7.0		7.5				5.9	
95% CI	4.3 to 5.3		3.8 to 4.6		4.6 to 5.6		6.7 to 8.2		6.6 to 7.5		6.9 to 8.1				5.7 to 6.2	
> 8.6 U/L	9/84	11	7/116	6	17/130	13	49/129	38	38/136	28	41/113	36			161/708	23
Testosterone, ng/L																
Mean	4.2		4.8		4.7		3.9		4.1		4.3				4.3	
95% CI	3.9 to 4.6		4.5 to 5.2		4.4 to 5.0		3.6 to 4.2		3.8 to 4.4		4.0 to 4.6				4.2 to 4.5	
< 2.8 ng/L	17/84	20	17/116	15	18/130	14	36/129	28	29/137	21	17/113	15			134/709	19
Aging Males' Symptoms scale																
Total score																
Mean	30.8		29.0		30.4		32.6		29.6		30.8				30.6	
95% CI	28.2 to 33.3		26.8 to 31.3		28.3 to 32.6		30.4 to 34.8		27.8 to 31.5		28.6 to 33.0				29.7 to 31.4	
Impairment†																
No (45%)	42/90	47	62/111	56	57/125	46	57/130	44	67/140	48	50/116	43			335/712	47
Little (37%)	19/90	21	25/111	23	42/125	34	32/130	25	39/140	28	36/116	31			193/712	27
Moderate (11%)	18/90	20	17/111	15	13/125	10	24/130	19	27/140	19	19/116	16			118/712	17
Severe (7%)	11/90	12	7/111	6	13/125	10	17/130	13	7/140	5	11/116	10			66/712	9
Utilization of cryopreserved sperm for ART, yes	3/26	12	0/48	0	1/53	2	8/47	17	7/54	13	7/46	15			26/274	10
Reproduction after therapy																
Birth after natural fertilization	7/76	9	11/104	11	4/112	4	0/117	0	2/131	2	0/112	0			24/652	4
Natural fertilization, but no birth (yet)	2/76	3	2/104	2	2/112	2	2/117	2	1/131	1	0/112	0			9/652	1
Birth after ART	0/76	0	0/104	0	0/112	0	4/117	3	3/131	2	3/112	3			10/652	2
ART, but no birth (yet)	1/76	1	0/104	0	0/112	0	4/117	3	3/131	2	4/112	4			12/652	2

Abbreviations: A(B)VD, doxorubicin, (bleomycin), vinblastine, and dacarbazine; ART, assisted reproduction; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; 2+2, two cycles of BEACOPP followed by two cycles of ABVD.

*Total No. represents number of patients with valid data, and percentages represent percentages of patients with valid data.

†Classification of Aging Males' Symptoms total score, with reference scores for German men > 40 years in parentheses.

DISCUSSION

With a total of 1,323 survivors of HL treated within the German Hodgkin Study Group HD13 to HD15 trials, to our knowledge, this is the largest detailed study on gonadal function and fertility after chemotherapy reported so far. The following major findings emerge from this analysis:

First, as expected, hormone levels correlate with the intensity of chemotherapy. In women, age was also a relevant factor for a reduced ovarian reserve. Normal mean AMH levels (> 2 μg/L) were observed in women younger than 30 years after two to four cycles of ABVD early-stage treatment, but AMH levels were compromised in survivors ≥ 30 years old. After treatment with six to eight cycles of BEACOPP, mean AMH levels were 0 μg/L in both age groups, and the highest FSH levels were measured in women older than 30 years.

In men, half of the survivors after early-stage treatment had FSH and inhibin B levels corresponding to proven fertile men, whereas

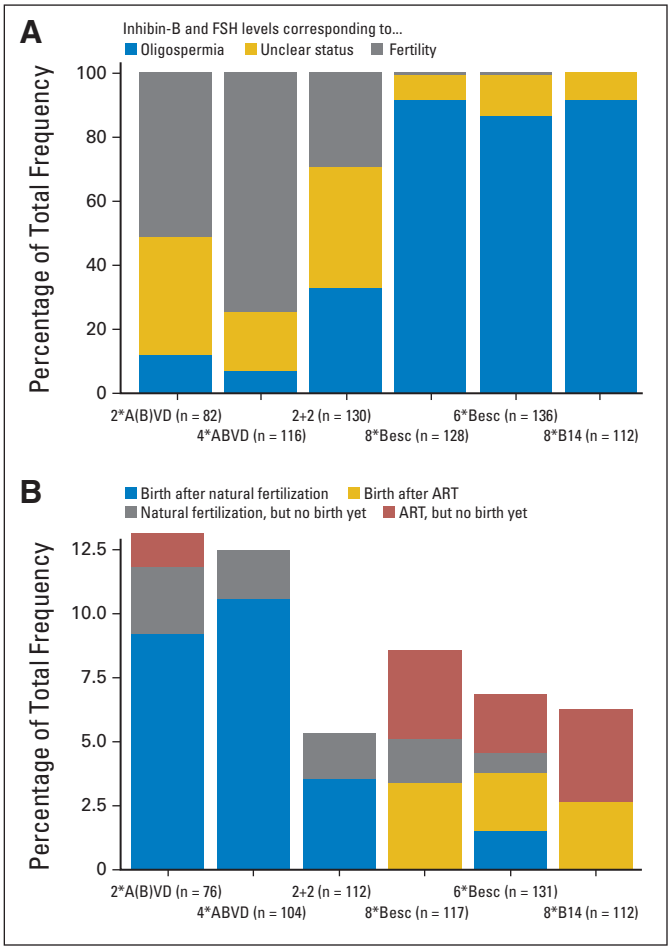

Fig 3. (A) Inhibin B and follicle-stimulating hormone (FSH) levels corresponding to proven fertility or to oligospermia in the three trials. (B) Reproduction in male survivors according to the three trials. A(B)VD, doxorubicin, (bleomycin), vinblastine, and dacarbazine; ART, assisted reproduction; B, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP); Besc, escalated BEACOPP; 2+2, two cycles of BEACOPP followed by two cycles of ABVD.

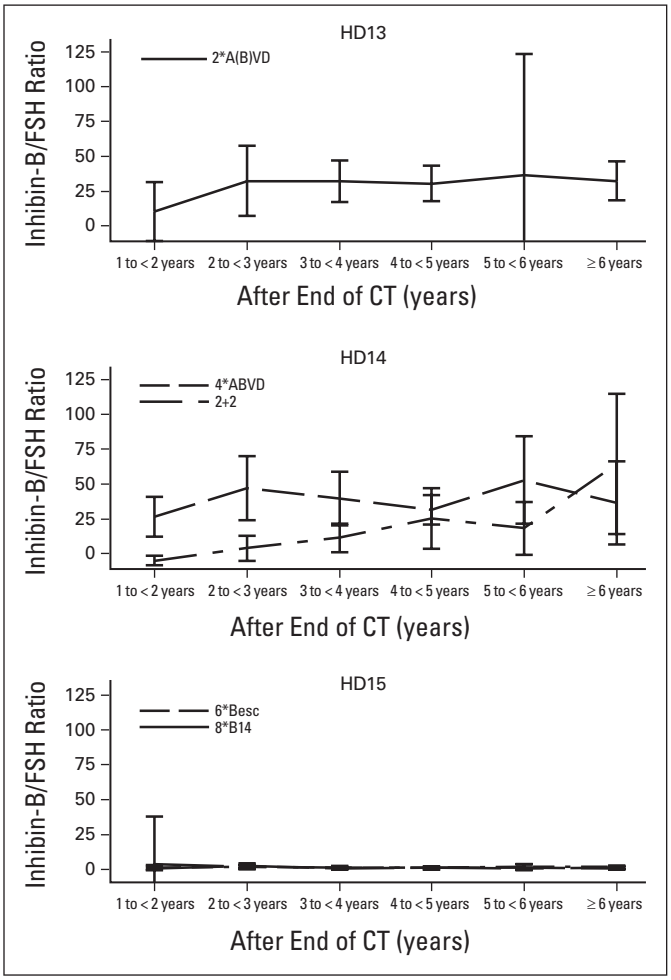

Fig 4. Effect of follow-up time on the inhibin B/follicle-stimulating hormone (FSH) ratio in the three trials. A(B)VD, doxorubicin, (bleomycin), vinblastine, and dacarbazine; B, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP); Besc, escalated BEACOPP; CT, chemotherapy; 2+2, two cycles of BEACOPP followed by two cycles of ABVD.

88.8% of survivors after advanced-stage treatment had levels corresponding to oligospermia. An effect of follow-up time on inhibin B and FSH levels was found in men after 2+2 treatment, suggesting a recovery up to 4 years after intermediate aggressive therapies. In contrast to the dose-dependent effect on the spermatogenesis as indicated by FSH and inhibin B, mean testosterone levels were within the normal range also after eight cycles of escalated BEACOPP.

Second, recovery of regular cycle was reported by more than 90% of women after early-stage treatment and was mostly completed within 1 year. In contrast, after treatment for advanced-stage HL, age at therapy onset was a decisive factor, and time to resumption of menstrual activity was considerably longer.

Third, compared with survivors after early-stage therapy, lower birth rates were observed in survivors after advanced-stage therapy (women: 15% *v* 6.5%, respectively; men: 7.2% *v* 3.3%, respectively). Of 52% of women and 32% of men with desire for children, only 15% and 12% reported parenthood within a median observation time of 4 years after advanced-stage therapy, respectively. Finally, female survivors older than age 30 years at diagnosis suffered three- to four-fold more frequently from severe menopausal symptoms compared with a 45- to 60-year-old German reference cohort.

The present analysis combines information from hormonal analyses with clinical data from large controlled trials and data obtained from standardized self-reported questionnaires. A portion of survivors did not respond, which might cause a bias. However, all information from our original trials indicated no major differences between participants and nonparticipants (Appendix Table A1). Also, comparable participation rates in all trials indicate a high external validity. We focused this analysis on the first years after chemotherapy, because gonadal toxicity, recovery, and finally parenthood are relevant problems within a limited time frame, especially for women.

As expected, chemotherapy-induced gonadal toxicity was highest after six to eight cycles of escalated BEACOPP(-14) in both female and male survivors of HL. After this regimen, hormonal levels reflect reduced ovarian reserve and amenorrhea indicates impaired fertility in the majority of women, and a relevant impairment of spermatogenesis occurred in the majority of men. However, in advanced-stage HL, aggressive therapy results in the highest overall survival rates reported

in large prospective trials.[1-3] Thus, balancing efficacy and toxicity is a difficult task for both patients and physicians. The detailed information from our analysis might contribute to a well-balanced shared decision-making process.

In women with cancer, AMH has been investigated as presumably valuable cycle-independent marker of the ovarian reserve.[23-30] In our analysis, AMH levels were significantly worse after more intensive alkylating agent–containing chemotherapy and with older age. This was also true for FSH values; however, FSH showed a better differentiation between the group of women with a regular cycle and the group suffering from amenorrhea after therapy. Additionally, in women younger than 30 years after advanced-stage HL, the mean AMH level was 0 μg/L. However, we observed pregnancies in women with low or even undetectable AMH levels, as previously reported in women without history of cancer.[31,32] These findings underline the need to further analyze the relevance of AMH assessment in female survivors of cancer. AMH is obviously not suited to predict fertility in individual patients. However, low AMH levels might indicate a reduced ovarian reserve and thus an increased risk of future premature ovarian failure. This risk cannot be estimated from our study because of the limited observation time.[33]

In addition, chemotherapy-induced amenorrhea might indicate infertility.[12] After advanced-stage treatment, age $\geq$ 30 years at diagnosis had the strongest impact on the risk of sustained amenorrhea 4 years after therapy. Surprisingly, in women younger than age 30 years, a high proportion (82%) reported a regular cycle despite escalated BEACOPP therapy. Nonetheless, overall, women face a relevant risk of infertility after BEACOPP chemotherapy. The protective effects of GnRH analogs observed after intermediate aggressive therapies (four cycles of ABVD or 2+2),[22] however, could not be documented after BEACOPP therapy for advanced-stage HL in this analysis. Finally, in the cohort of women $\geq$ 30 years old at diagnosis, we found a surprisingly high proportion of women with severe menopausal symptoms.[18] Again, age itself had a stronger negative impact on menopausal symptoms than treatment intensity. Interestingly, only 48.9% of women with severe symptoms were on hormone medication at the time of the survey. Because menopausal symptoms often substantially affect women's quality of life and might be easy to ameliorate with hormonal replacement therapy, this finding definitively needs further investigation.

In male survivors, we found a high proportion (88.8%) of oligospermia, indicated by FSH and inhibin B levels, after six to eight cycles of BEACOPP. Even only two cycles of escalated BEACOPP in the 2+2 regimen induced a marked decrease in the proportion of patients having hormone levels corresponding to proven fertile men (25%) compared with four cycles of ABVD (50%). This finding underscores the lower gonadotoxic potential of the ABVD regimen.[34-36] Only 30% of male survivors after advanced-stage therapy reported desire for children at 4 years. This observation time might be too short to finally judge on paternity, which was documented in only 12 men (two after natural fertilization and 10 after assisted reproduction). Thus, to maintain the chance for assisted reproduction, cryopreservation of sperm or testicular sperm extraction must be offered before starting aggressive therapy.[37] Interestingly, levels of testosterone were also within the normal range after escalated BEACOPP therapy, supporting the hypothesis that Leydig cells are more resistant to cytotoxic chemotherapy.[11,34,38,39] Also, mean aging male symptoms were within the normal range in our analysis.

To summarize, survivors after BEACOPP treatment for advanced-stage disease have the highest risk for symptomatic gonadal dysfunction. However, data directly comparing six to eight cycles ABVD to six to eight cycles of escalated BEACOPP in patients with HL should be generated to exactly quantify risk of treatment options in the context of gonadal toxicity. Until then, the information derived from our analysis may improve both the shared decision-making process regarding individual treatment decisions and the guidance during survivorship.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Manuscript writing: All authors

Final approval of manuscript: All authors

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